ORIGINAL ARTICLE

Ablative Fractional Laser-assisted Low-irradiance Photodynamic Therapy for Treatment of Actinic Keratoses in Organ Transplant Recipients: A Prospective, Randomized, Intraindividual Controlled Trial

Anke S. LONSDORF[1,2], Aric KELLER[1], Julia HARTMANN[1], Alexander H. ENK[1,2] and Patrick GHOLAM[1]
[1]Department of Dermatology, Ruprecht-Karls-University of Heidelberg and [2]National Center for Tumor Diseases Heidelberg, Heidelberg, Germany

Pain and inferior efficacy are major limiting factors of conventional photodynamic therapy for the field treatment of actinic keratoses in immunosuppressed organ transplant recipients. This prospective randomized controlled study evaluates the efficacy and tolerability of ablative fractional laser system pretreatment combined with low-irradiance photodynamic therapy (18.5 mW/cm²) compared with conventional photodynamic therapy (61.67 mW/cm²) in the treatment of actinic keratoses on the face and scalp in organ transplant recipients, using a red light-emitting diode lamp at a total light dose of 37 J/cm². Low-irradiance photodynamic therapy combined with Er:YAG pretreatment achieved a significantly superior lesion response rate (mean ± standard deviation 77.3 ± 23.6%) compared with conventional photodynamic therapy (61.8 ± 21.4%; $p = 0.025$) in intra-individual fields at 3 months without negatively impacting pain ($p = 0.777$) or cosmetic outcome ($p = 0.157$).

Key words: actinic keratosis; immunosuppression; keratinocyte cancer; organ transplant recipients; photodynamic therapy.

Accepted Mar 31, 2022; Epub ahead of print Mar 31, 2022

Acta Derm Venereol 2022; 102: adv00694.

DOI: 10.2340/actadv.v102.1057

Corr: Anke S. Lonsdorf, Department of Dermatology, Ruprecht-Karls-University of Heidelberg, Im Neuenheimer Feld 440, DE-69120 Heidelberg, Germany. E-mail: anke.lonsdorf@med.uni-heidelberg.de

SIGNIFICANCE

Long-term immunosuppressed organ transplant recipients are at high risk of developing multiple keratinocyte cancers that tend to behave more aggressively than in the general population. This study demonstrates that, compared with conventional photodynamic therapy, low-irradiance photodynamic therapy combined with ablative Er:YAG laser pretreatment is a significantly more efficient and similarly well-tolerated therapeutic option for multiple actinic keratoses in difficult-to-treat immunosuppressed organ transplant recipients.

Keratinocyte cancer (KC), particularly cutaneous squamous cell carcinoma (SCC), is a major source of morbidity and mortality in long-term iatrogenic immunosuppressed patients. There is a more than 65-fold increased incidence of KC in organ transplant recipients (OTR) compared with the general population (1–3).

Clinical studies have shown that SCC are almost always associated with actinic keratoses (AK), an *in situ* precursor lesion of SCC (4–6), and that the risk of surrounding skin to develop SCC is reduced if AK are treated (7). The disease burden in the post-transplantation phase is high, with AK and Bowen's disease affecting up to 40% of OTR within 5 years of transplantation (3, 8). Furthermore, the management of post-transplant SCC is typically complicated by a more aggressive clinical course, a characteristically high tumour burden, and worse prognosis, compared with the general population (1–3, 9, 10). Thus, a proactive and efficient therapeutic approach for treatment of AK and severely photodamaged skin in OTR is essential to prevent possibly extensive cutaneous carcinogenesis (11–13).

Conventional lesion-by-lesion directed treatments of AK, such as excision, cryotherapy, topical 5-fluorouracil or imiquimod, are of reduced practical value in OTR is due to restricted approval in immunosuppressed patients, or the typically extensive field cancerization (2, 13, 14). In this context, conventional photodynamic therapy (c-PDT) with 5-aminolaevulinic acid (ALA) or methylaminolaevulinate (MAL) advanced as a safe, efficacious, and mostly well-tolerated, treatment modality for larger photodamaged fields and multiple AK in both non-transplant patients and OTR (4, 15–18). In topical c-PDT, ALA or its methylated ester, MAL, both precursors of the endogenous photosensitizer protoporphyrin IX (PpIX) is applied to the skin. After 3 h incubation, the generation of reactive singlet oxygen upon photoactivation of the accumulated PpIX by irradiation with visible light, induces apoptosis, necrosis and a subsequent inflammatory response in the target lesions (19). In OTR under iatrogenic immunosuppression (IS), however, inferior response rates of c-PDT compared with non-transplant patients, and increased pain during irradiation are the major limitations for c-PDT, particularly in field-cancerized skin and lesions located in the face and scalp region (14, 20). Thus, as requested by a pan-European group of dermatology experts, there is a high need to evaluate specific PDT protocols for optimizing outcomes in the high-risk patient population of OTR (4).

In non-transplant patients, enhanced efficacy of c-PDT has been reported by pretreatment with an ablative fractional laser system (AFL-PDT) with superior 3-month lesion response rates (LRR) ranging from 86.9% to 88% compared with 59% to 61.2% for c-PDT (21, 22). C-PDT efficacy is critically dependent on the penetration and accumulation of the PpIX precursors and thus reduced when treating particularly hyperkeratotic AK (23). AFL is thought to facilitate MAL penetration into the skin by creating microscopic vertical channels that disrupt the stratum corneum barrier, thereby enhancing the accumulation of PpIX and PDT efficacy (24–26). Superior efficacy of AFL-PDT compared with c-PDT has been reported even for the treatment of microinvasive SCC (27), suggesting that AFL-PDT may be a particularly valuable treatment modality for patients with severe field cancerization. Yet, while optimizing the efficacy of PDT short-term side-effects, particularly pain, are equally increased during AFL-PDT (21, 22).

We demonstrated previously, in non-transplant patients, that pain during PDT irradiation can be significantly reduced without limiting its therapeutic efficacy, by reducing the irradiance while maintaining a fluence of 37 J/cm^2 (low-irradiance PDT; li-PDT) (28). Thus, a combination of these treatment modalities as ablative fractional laser-assisted low-irradiance PDT (AFL-li-PDT) seems a promising therapeutic concept for patients at particularly high risk of extensive skin carcinogenesis and treatment-associated pain, such as OTR.

The aim of the current prospective randomized controlled, open-label study, with intra-individual control in a half-side comparative design, was to evaluate the efficacy and tolerability of AFL-li-PDT compared with c-PDT for the treatment of AK in long-term-immunosuppressed OTR.

METHODS

Patient population and study design

A total of 18 OTR, aged >18 years, under active IS and with clinically or histological confirmed AK on the scalp or face were included in the study between November 2020 and May 2021 at the Department of Dermatology at the University of Heidelberg. To control for interpatient variability, participants were required to present with 2 clinically comparable areas of photodamaged skin and AK on anatomically diametrical sites, serving as intra-individual control for AFL-li PDT or c-PDT, respectively. Patients were questioned about their skin cancer history, prior treatments for skin cancer, including AK, and immunosuppressive therapy regimen. Electronic medical records were reviewed to confirm and complement this information.

Patients were randomized 1:1 into the 2 groups (A or B, $n=9$/group). All patients underwent both PDT protocols (c-PDT and AFL-li-PDT), each protocol being conducted on a separate day and on anatomically diametrical, separate sites. Treatment groups differed solely in the order of the 2 treatment protocols, with patients in group A first undergoing c-PDT, followed by AFL-li-PDT on the anatomically diametrical site, whereas patients in group B were treated with AFL-li-PDT followed by c-PDT. The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (# S-347/2020) and all participants provided written, informed consent prior to enrollment in the study.

Photodynamic therapy (PDT)

Conventional PDT (c-PDT). After gentle curettage of the hyperkeratotic lesions, the photosensitizer Metvix® (5-aminolaevulinic acid methylester (MAL); Galderma, Düsseldorf, Germany) was applied on the entire treatment area, covered with an occlusive, opaque dressing. After a 3-h incubation the bandage was removed and the photosensitizer wiped off gently. Directly thereafter, irradiation was performed using a red light-emitting diode (LED) lamp (BF-RhodoLED®, Biofrontera, Leverkusen, Germany) with a peak emission of 635 nm, using a total light dose of 37 J/cm2. Intensity was set to 100%, corresponding to an irradiance of 61.67 mW/cm^2. Standard irradiation time was 10 min.

Ablative fractional laser low-irradiance PDT (AFL-li-PDT). Prior to curettage or laser treatment a topical anaesthetic (25 mg/g lidocaine, 25 mg/g prilocaine, EMLA®, Aspen Germany GmbH) was applied on the treatment area. After an incubation time of 30 min the hyperkeratotic lesions underwent gentle curettage. Consecutively, AFL pretreatment was performed (treatment parameter C10%, 10×4.0 J/cm^2, 100 µs, 1 pass) on the complete treatment area using an Er:YAG laser system (MCL 31 Dermablate, Asclepion Laser Technologies, Jena, Germany). Immediately after AFL pretreatment the photosensitizer Metvix® (5-aminolaevulinic acid methylester (MAL); Galderma, Düsseldorf, Germany) was applied on the entire treatment area covered with an occlusive, opaque dressing. After an incubation of 3 h the bandage was removed and the photosensitizer wiped off gently. Directly thereafter, irradiation was performed using a red LED lamp (BF-RhodoLED®, Biofrontera, Leverkusen, Germany) with a peak emission of 635 nm using a total light dose of 37 J/cm^2. Intensity was set to 30% corresponding to an irradiance of 18.5 mW/cm^2. Standard irradiation time was 33 min and 20 s.

Evaluation of clinical efficacy, pain and cosmetic outcome

Oral analgesics, mostly standardized to a single oral dose 1 g metamizole, were administered 30 min prior to irradiation. During irradiation the treatment area was continuously cooled with a cold-air fan (CRIOjet Air C50, Linde Gas Therapeutics GmbH, Niefern-Öschelbronn, Germany). Patients were offered short interruptions from irradiation if the pain was too intense, and treatment was continued immediately after pain relief. Patients were asked to score the experienced pain during the irradiation period by means of a 10-cm visual analogue scale (VAS) graded from 0 (no pain) to 10 (unbearable pain) immediately after treatment. The number of treatment interruptions, as requested by the patient, and time to first treatment interruption were used as secondary surrogate indicators for pain.

Immediately before PDT and at a clinical follow-up visit 3 months after PDT, each treatment area was photographed, AK were mapped, counted, and graded by a dermatologist, as proposed by Olsen et al. (29), according to the thickness of the lesions: grade I AK are slightly palpable, grade II are moderately thick, and grade III AK are very thick and/or obvious. Furthermore, the AK area and severity index (AKASI), as proposed by Dirschka et al. (30), was determined. Briefly, the disease severity of each area was evaluated using a quantitative scale ranging from 0 (none) to 4 (severe) for 3 clinical characteristics of AK (i.e. distribution, erythema and thickness). The percentage of the area affected was then determined and assigned to the corresponding score values from 0 to 6. The sum of the 4 scores is multiplied by the area coefficient to obtain a subscore for each area of the head. According to the split-face design of the study only half of the forehead and half of the scalp were treated with one method. Therefore, the area

coefficients were modified. Treatment of half of the face or half of the scalp was given a weighting of 20%, while a weighting of 10% was assigned to half of the forehead.

For evaluation of the clinical efficacy, the AKASI reduction and the absolute reduction in AK were assessed for each group at the 3-month follow-up visit. The individual LRR was calculated as the difference in AK before and 3 months after PDT, divided by the number of AK before PDT. The clinical follow-up visits at 3 months after PDT further included recording of side-effects and assessment of the cosmetic outcome by a dermatologist using a 4-point Likert item (1: poor, 2: moderate, 3: good, 4: excellent). In addition, patients were questioned about their overall preferred treatment protocol.

Statistical analysis

A sample size of 18 patients per group to be enrolled in the study was calculated using PASS (Version 16.0.3, NCSS, Kaysville, UT, USA), assuming a difference of 0.2 points on the mean LRR of both groups, assuming an SD of 0.25 with a power of 80% at a 2-sided significance level of 0.05 and accounting for an assumed 10% drop-out rate.

As both treatment regimens are applied to the same patients (dependent samples) and the distribution of the mean LRR in the intervention group is unknown, this 2-sided hypothesis was evaluated using the Wilcoxon signed-rank test. Primary analysis was based on the intention-to-treat population, including all randomized patients. Categorical data are presented as frequencies and percentages. For continuous data, *n*, mean and standard deviation (SD) are provided. AKASI reduction, pain scores, and cosmetic outcome were analysed using the Wilcoxon signed-rank test. Differences in mean AKASI or mean number of AK before and 3 months after PDT between both treatment groups were analysed using the Wilcoxon-signed-rank test. Differences in the number of treatment interruptions and the preferred regimen were analysed descriptively. All analyses were carried out using SPSS (Version 26, IBM, Armonk, NY, USA). *p*-values <0.05 were considered significant.

Table I. Demographic and medical characteristics of the study population ($n=18$)

Characteristics	
Age, years, mean ± SD	63.5 ± 8.8
Sex, *n* (%)	
Male	17 (94.4)
Female	1 (5.6)
Age at Tx, years, mean ± SD	46.1 ± 13.6
Type of transplanted organ, *n* (%)	
Kidney	13 (72.2)
Liver	3 (16.7)
Heart	1 (5.6)
Lung	1 (5.6)
Duration of immunosuppression, years, mean ± SD	17.5 ± 13.1
Immunosuppression regimen, *n* (%)	
Methylprednisolone	15 (83.3)
Tacrolimus	11 (61.1)
Mycophenolate mofetil	10 (55.6)
Cyclosporine	5 (27.8)
Azathioprine	3 (16.7)
mTOR inhibitor	2 (11.1)
Skin cancer history	
Actinic keratosis, *n* (%)	18 (100)
Bowen's disease, *n* (%)	17 (94.4)
SCC, *n* (%); mean ± SD	13 (72.2); 7.9 ± 9.2
BCC, *n* (%); mean ± SD	12 (66.7); 3.8 ± 3.7
Invasive KC, *n* (%); mean ± SD	16 (88.9); 11.7 ± 11.4
Kaposi sarcoma, *n* (%)	1 (5.6)
Melanoma; Merkel cell carcinoma, *n* (%)	0 (0)
Lymph node metastasis of cutaneous SCC, *n* (%)	2 (11.1)
First actinic keratosis since Tx, years, mean ± SD	8.7 ± 9.8
First invasive KC since Tx, years, mean ± SD	9.3 ± 9.5
Previous skin cancer therapies, *n* (%)	
Surgery	18 (100)
Photodynamic therapy	9 (50)
Laser therapy	1 (5.6)
Cryotherapy	3 (16.7)
Topical therapy	13 (72.2)
Imiquimod	9
5-Fluorouracil	4
Ingenol mebutate	10
Diclofenac sodium	4

SCC: squamous cell carcinoma; BCC: basal cell carcinoma; KC: keratinocyte cancer; SD: standard deviation; Tx: organ transplantation.

RESULTS

Clinicopathological characteristics of the study population

Table I informs about clinicopathological characteristics of the 18 OTR included in this study. Participants received maintenance immunosuppressive therapy according to organ-specific treatment protocols, in line with institutional and international guidelines. The treatments were mostly combinations of calcineurin inhibitors, mycophenolate mofetil and low-dose glucocorticosteroid. All OTR had a history of previous AK, and 88.9% had a history of invasive KC, predominantly SCC (72%, mean ± SD number: 7.9 ± 9.2). 50% of OTR had a history of >9 cumulative invasive KC (11.7 ± 11.4). Two participants had been treated previously for cervical lymph node metastasis of cutaneous SCC.

Efficacy

Both intra-individual treatment fields before PDT were clinically comparable with no significant differences regarding total numbers of AK at baseline and distribution of AK grades I–III in c-PDT-treated and AFL-li-PDT-treated fields. In total, 172 AK, predominantly AK grades I and II, were treated (**Table II**).

At 3 months after treatment, a significant decrease in the absolute number of AK was noted in both treatment groups (c-PDT: $p<0.0005$; AFL li-PDT: $p<0.0005$) (Table II). Of particular note, a significantly higher mean ± SD LRR of 77.3 ± 23.6% was achieved by AFL-li-PDT compared with c-PDT (61.8 ± 21.4%; $p=0.025$) at 3 months (Table II and **Fig. 1**A). While not reaching statistical significance, a trend towards an increased AKSI reduction was correspondingly achieved in AFL-li-PDT treated fields compared with c-PDT-treated fields after 3 months (Table II and Fig. 1B).

Pain

Experienced pain according to VAS scoring did not differ significantly between AFL-li-PDT and c-PDT (Table II and Fig. 1C). Patient requests for brief treatment interruptions, as a surrogate marker for experienced pain during irradiation, were somewhat more frequent in the group of AFL-li-PDT compared with c-PDT. While

Table II. Clinical characteristics of intra-individual treatment fields at baseline, therapeutic efficacy and cosmetic outcome measured 3 months after c-PDT and AFL-li-PDT and assessment of PDT-associated pain

	c-PDT	AFL-li-PDT	*p*-value[a]
Number of patients	18		
Site, *n* (%)			
Face Scalp Forehead	3 (16.7) 6 (33.3) 9 (50.0)		
Treatment area, cm^2, mean±SD	128.7±49.3		
Lesion count, mean±SD			
Actinic keratosis total baseline	5.0±1.7	4.6±1.7	0.267
Grade I	1.9±1.3	1.7±1.6	0.458
Grade II	2.4±1.8	2.4±1.9	0.365
Grade III	0.6±1.0	0.5±0.9	0.564
Actinic keratosis total after PDT	2.1±1.6	1.1±1.1	**0.009**
Grade I	1.4±1.4	0.4±0.5	
Grade II	0.6±0.9	0.3±0.8	
Grade III	0.2±0.5	0.3±0.6	
Lesion response rate, %, mean±SD	61.8±21.4	77.3±23.6	**0.025**
AKASI, mean±SD			
Baseline	1.1±0.6	1.1±0.5	0.888
After photodynamic therapy	0.7±0.4	0.5±0.5	0.054
AKASI reduction, %, mean±SD	41.4±23.3	54.4±33.4	0.132
Cosmetic outcome, mean±SD	3.2±0.5	3.4±0.5	0.157
Pain			
Visual analogue scale, mean±SD	5.0±2.4	5.2±3.0	0.777
Treatment interruptions, *n* (%)	3 (16.7)	5 (27.8)	
Premature treatment termination, *n* (%)	0	2 (11.1)	

[a]Wilcoxon signed-rank test.
AFL-li-PDT: ablative fractional laser-assisted low-irradiance photodynamic therapy; AKASI: actinic keratosis area and severity index; c-PDT: conventional photodynamic therapy; SD: standard deviation.
A *p*-value < 0.05 was considered significant (shown in bold).

most patients coped well with any discomfort during irradiation, 2 patients requested early termination of the irradiation during AFL-li-PDT (Table II).

Cosmetic outcome, patient preference and systemic side-effects

Cosmetic outcome, as assessed by a dermatologist 3 months after PDT, was rated overall "good" (61%) to "excellent" (36%) across all treatment fields. One patient achieved only "moderately good" cosmetic outcome in his c-PDT-treated field, but "good" cosmetic outcome in his AFL-li-PDT-treated field. In general, cosmetic outcome in AFL-li-PDT-treated fields ("excellent": 8 patients; "good": 10 patients) tended to be more favourable compared with c-PDT-treated intra-individual fields ("excellent": 5 patients, "good": 12 patients) (Table II).

Patients stated no significantly different preference for any the treatment protocols (c-PDT: 38.9%, $n=7$; AFL-li-PDT: 27.8%, $n=5$; both similar: 27.8%, $n=5$). One patient stated he would refrain from any PDT treatment (5.6%). No therapy-associated systemic side-effects were noted on the day of treatment or during the follow-up period.

DISCUSSION

Effective treatment of the typically extensive field cancerization in OTR, particularly on the face and scalp, is an integral part of the advised proactive risk-adapted dermatological care for these high-risk patients, but poses a major challenge in clinical practice.

While previous studies demonstrated the efficacy and safety of c-PDT in the treatment of AK in both non-transplant and immunocompromised transplant patients, pain and reduced efficacy are the main limitations, particularly in OTR (4, 15, 17, 18, 20, 31, 32).

This is the first prospective randomized controlled study assessing the efficacy and tolerability of AFL-li-PDT compared with c-PDT for AK treatment on the scalp and face in immunosuppressed OTR, aiming at increased efficacy without intensifying pain during irradiation in these difficult-to-treat patients.

Although direct comparison of reported data are commonly hampered by the use of varied light sources, inconstant dosages, different follow-up times and the lack of intra-individual controls, previous studies in OTR have reported 3-month response rates of 50–60% following a single MAL c-PDT session (4, 13, 14, 16, 33), which is in accordance with a 62.6% LRR achieved in c-PDT fields in the current study.

Increased efficacy of PDT has been previously reported for AFL drug delivery penetration pretreatment (21, 22, 33). However, pain is typically more intense after AFL pretreatment (22) and poses the most frequent and limiting short-term side-effect of PDT, resulting in reduced

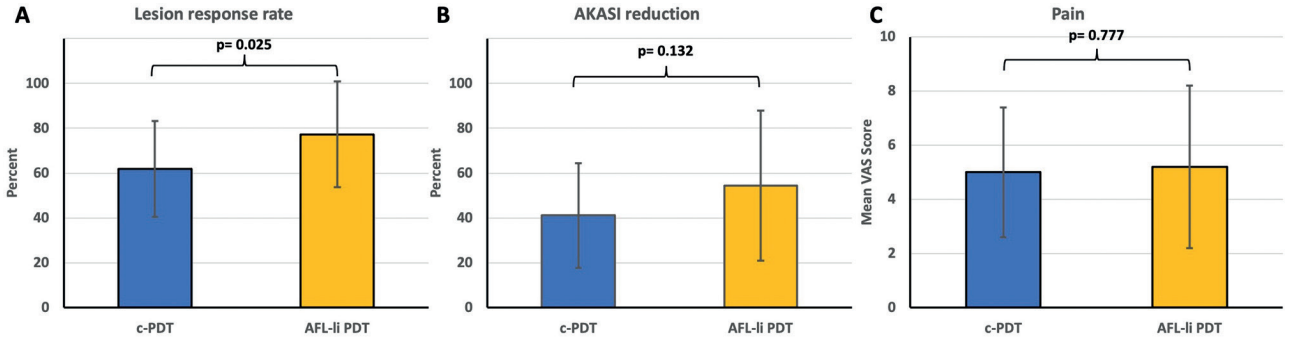

Fig. 1. Therapeutic efficacy of ablative fractional laser assisted low-irradiance photodynamic therapy (AFL-li-PDT) compared with conventional PDT (c-PDT) as assessed by: (A) the lesion response rate; (B) actinic keratosis area and severity index (AKASI) reduction 3 months after treatment; and (C) experienced pain according to the visual analogue scale (visual analogue scale (VAS); range 0–10) in both treatment groups. Whiskers represent ±1 standard deviation (SD). Wilcoxon signed-rank test. A *p*-value < 0.05 was considered significant.

patient satisfaction and compliance with future PDT treatments (32, 34).

Traditional strategies to counter pain during irradiation including cold-air fans, topical analgesics, infiltration anaesthesia or nerve block are often non-satisfying or challenging to realize in clinical practice (32, 35). Against this background, we recently demonstrated significantly reduced pain without limiting the therapeutic efficacy compared with c-PDT in non-transplant patients, by reducing the irradiance to 25% while maintaining the same total light dose in li-PDT (28). The current study demonstrates that AFL-li-PDT, which combines the higher therapeutic efficacy of AFL pretreatment with the superior tolerability of li-PDT, can achieve significantly enhanced clinical response with a mean LRR of 73.3% compared with c-PDT ($p = 0.025$) in difficult-to-treat OTR without significantly increasing pain during irradiation. Furthermore, we found an overall lower mean AKASI reduction in c-PDT-treated fields compared with a previous c-PDT study in non-transplant patients (36), but a trend towards a superior mean AKSI reduction by AFL-li-PDT compared with c-PDT in the current study.

Togsverd-Bo et al. (33) previously combined AFL with typically less painful daylight-mediated photodynamic therapy (AFL-dl-PDT) for AK treatment in OTR and reported enhanced efficacy with 74% 3-month LRR compared with dl-PDT and reduced pain compared with c-PDT. As a drawback, depending on weather conditions or low temperature, dl-PDT cannot be conducted year-round in northern Europe (37), which may limit the practicability of AFL-dl-PDT by complicating scheduling of combined AFL and dl-PDT treatment sessions, particularly for high-risk patients in need of timely treatment of AK and patients with comorbidities who require frequent medical care.

In addition to the type and duration of irradiation being established influencing factors of pain during PDT (28, 31, 38), predictive factors for increased pain include age > 70 years, lesion size and redness, treatment for AK on the head and scalp and for large areas of field cancerization (4, 32, 34, 39). In addition, OTR seem to be more severely affected than non-transplant patients by pain during PDT treatment, possibly reflecting their typically more extensive field cancerization (14, 40). In the current study, a noteworthy 50% of OTR had a history of 10 or more previous invasive KC, predominantly SCC (11.08 ± 9.08), with 2 patients developing metastatic SCC to the cervical lymph nodes, reflecting the substantial morbidity and severity of field cancerization in the current patient sample.

Yet, while patient-requested interruptions were more frequent during the prolonged irradiation period of AFL-li-PDT, experienced pain was not significantly enhanced during highly effective AFL-li-PDT irradiation compared with c-PDT in these difficult-to-treat patients. However, treatment-related pain was still moderately high during both c-PDT (mean ± SD VAS 5.0 ± 2.4) and AFL-li-PDT (5.2 ± 3.0), thus emphasizing the need for further research on effective pain-controlling therapies and adjustment of AFL-li-PDT parameters, such as further reducing irradiance, continuous LED irradiation over a more prolonged time period and/or lower initial irradiance, to identify the optimal procedure parameters that mitigate treatment-related pain at no loss of efficacy. Notably, AFL-li-PDT yielded excellent cosmesis and high patient acceptance in the current study, and systemic side-effects were not noted for any of the treatment protocols.

Assessing the efficacy and tolerability of AFL-li-PDT compared with c-PDT for the treatment of AK in a German OTR population this study has important strengths, including the randomized study design with intra-individual control. Some limitations of the current study, however, should be noted. In line with previous studies (18, 20, 33) the current study population included predominantly male OTR. Furthermore, grade I and grade II AK were more frequent compared with grade III AK in the current patients, which reflects their close dermato-oncological surveillance in our specialized dermatology outpatient clinic for immunosuppressed patients, but limits the informative value of the observed treatment efficacy for more hyperkeratotic lesions. Efficacy evaluation after a longer follow-up period or cyclic AFL-li-PDT treatment would be desirable, but is often hampered in these high-risk patients by their need for frequent and proactive treatment for KC and precursor lesions in areas of field cancerization. While the current study demonstrates the clinical efficacy, tolerability and safety of AFL-li-PDT for the treatment of AK in immunosuppressed OTR, further studies are required to assess the impact of AFL-li-PDT on AK transformation and SCC incidence in this high-risk population.

In conclusion, AFL-li-PDT represents a promising therapeutic option, with good tolerability and cosmetic outcome and superior clinically efficacy after 3 months compared with c-PDT, for difficult-to-treat OTR with multiple AK on the face and scalp.

ACKNOWLEDGEMENTS

The authors thank the participating patients and staff of the dermatology outpatient clinic for immunosuppressed patients at the National Center for Tumor Diseases Heidelberg (NCT) and the staff of the Department of Dermatology at the University Hospital Heidelberg for their valuable contribution to this research.

Conflicts of interest: AEH receives funding by grant SFB/TR 156 of the DFG (Deutsche Forschungsgemeinschaft) and payment or honoraria by Janssen-Cilag, Biotest, MSD and Galderma. AEH is president of the European Dermatology Forum (EDF). ASL, AK, JH and PG have no conflicts of interest to declare.

REFERENCES

1. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003; 348: 1681–1691.
2. Berg D, Otley CC. Skin cancer in organ transplant recipients:

epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002; 47: 1–17; quiz 18–20.
3. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011; 65: 253–261.
4. Basset-Seguin N, Baumann Conzett K, Gerritsen MJ, Gonzalez H, Haedersdal M, Hofbauer GF, et al. Photodynamic therapy for actinic keratosis in organ transplant patients. J Eur Acad Dermatol Venereol 2013; 27: 57–66.
5. Czarnecki D, Meehan CJ, Bruce F, Culjak G. The majority of cutaneous squamous cell carcinomas arise in actinic keratoses. J Cutan Med Surg 2002; 6: 207–209.
6. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988; 1: 795–797.
7. Mittelbronn MA, Mullins DL, Ramos-Caro FA, Flowers FP. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol 1998; 37: 677–681.
8. Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M, et al. Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol 1995; 33: 222–229.
9. Hartmann J, Schuler S, Enk AH, Lonsdorf AS. Skin cancer in organ transplant recipients: dynamics in the incidence and clinical predictors for the first and subsequent post-transplant non-melanoma skin cancer. J Eur Acad Dermatol Venereol 2019; 33: 1281–1289.
10. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, Bataille V, Bastholt L, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 1. epidemiology, diagnostics and prevention. Eur J Cancer 2020; 128: 60–82.
11. Cohen JL. Actinic keratosis treatment as a key component of preventive strategies for nonmelanoma skin cancer. J Clin Aesthet Dermatol 2010; 3: 39–44.
12. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000; 42: 23–24.
13. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011; 65: 263–279.
14. Wlodek C, Ali FR, Lear JT. Use of photodynamic therapy for treatment of actinic keratoses in organ transplant recipients. Biomed Res Int 2013; 2013: 349526.
15. Markham T, Collins P. Topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratoses. Br J Dermatol 2001; 145: 502–504.
16. Dragieva G, Prinz BM, Hafner J, Dummer R, Burg G, Binswanger U, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol 2004; 151: 196–200.
17. Dragieva G, Scharer L, Dummer R, Kempf W. Photodynamic therapy – a new treatment option for epithelial malignancies of the skin. Onkologie 2004; 27: 407–411.
18. Liew YCC, De Souza NNA, Sultana RG, Oh CC. Photodynamic therapy for the prevention and treatment of actinic keratosis/squamous cell carcinoma in solid organ transplant recipients: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2020; 34: 251–259.
19. Noodt BB, Berg K, Stokke T, Peng Q, Nesland JM. Apoptosis and necrosis induced with light and 5-aminolaevulinic acid-derived protoporphyrin IX. Br J Cancer 1996; 74: 22–29.
20. Dragieva G, Hafner J, Dummer R, Schmid-Grendelmeier P, Roos M, Prinz BM, et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. Transplantation 2004; 77: 115–121.
21. Ko DY, Jeon SY, Kim KH, Song KH. Fractional erbium: YAG laser-assisted photodynamic therapy for facial actinic keratoses: a randomized, comparative, prospective study. J Eur Acad Dermatol Venereol 2014; 28: 1529–1539.
22. Togsverd-Bo K, Haak CS, Thaysen-Petersen D, Wulf HC, Anderson RR, Haedersdal M. Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: a randomized clinical trial. Br J Dermatol 2012; 166: 1262–1269.
23. Tyrrell JS, Campbell SM, Curnow A. The relationship between protoporphyrin IX photobleaching during real-time dermatological methyl-aminolevulinate photodynamic therapy (MAL-PDT) and subsequent clinical outcome. Lasers Surg Med 2010; 42: 613–619.
24. Haedersdal M, Sakamoto FH, Farinelli WA, Doukas AG, Tam J, Anderson RR. Fractional CO(2) laser-assisted drug delivery. Lasers Surg Med 2010; 42: 113–122.
25. Haedersdal M, Katsnelson J, Sakamoto FH, Farinelli WA, Doukas AG, Tam J, et al. Enhanced uptake and photoactivation of topical methyl aminolevulinate after fractional CO2 laser pretreatment. Lasers Surg Med 2011; 43: 804–813.
26. Forster B, Klein A, Szeimies RM, Maisch T. Penetration enhancement of two topical 5-aminolaevulinic acid formulations for photodynamic therapy by erbium:YAG laser ablation of the stratum corneum: continuous versus fractional ablation. Exp Dermatol 2010; 19: 806–812.
27. Choi SH, Kim KH, Song KH. Effect of methyl aminolevulinate photodynamic therapy with and without ablative fractional laser treatment in patients with microinvasive squamous cell carcinoma: a randomized clinical trial. JAMA Dermatol 2017; 153: 289–295.
28. Gholam P, Bosselmann I, Enk AH, Dick J. Low irradiance compared with conventional photodynamic therapy in the treatment of actinic keratoses. Photodermatol Photoimmunol Photomed 2019; 35: 110–115.
29. Olsen EA, Abernethy ML, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. J Am Acad Dermatol 1991; 24: 738–743.
30. Dirschka T, Pellacani G, Micali G, Malvehy J, Stratigos AJ, Casari A, et al. A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index. J Eur Acad Dermatol Venereol 2017; 31: 1295–1302.
31. Fink C, Enk A, Gholam P. Photodynamic therapy – aspects of pain management. J Dtsch Dermatol Ges 2015; 13: 15–22.
32. Borgia F, Giuffrida R, Caradonna E, Vaccaro M, Guarneri F, Cannavo SP. Early and late onset side effects of photodynamic therapy. Biomedicines 2018; 6: 12.
33. Togsverd-Bo K, Lei U, Erlendsson AM, Taudorf EH, Philipsen PA, Wulf HC, et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients – a randomized controlled trial. Br J Dermatol 2015; 172: 467–474.
34. Steinbauer JM, Schreml S, Babilas P, Zeman F, Karrer S, Landthaler M, et al. Topical photodynamic therapy with porphyrin precursors – assessment of treatment-associated pain in a retrospective study. Photochem Photobiol Sci 2009; 8: 1111–1116.
35. Fink C, Uhlmann L, Enk A, Gholam P. Pain management in photodynamic therapy using a nitrous oxide/oxygen mixture: a prospective, within-patient, controlled clinical trial. J Eur Acad Dermatol Venereol 2017; 31: 70–74.
36. Schmitz L, von Dobbeler C, Gupta G, Gambichler T, Szeimies RM, Morton CA, et al. Photodynamic therapy leads to significant improvement of actinic keratosis area and severity index (AKASI). Photodiagnosis Photodyn Ther 2018; 21: 66–70.
37. Morton CA, Wulf HC, Szeimies RM, Gilaberte Y, Basset-Seguin N, Sotiriou E, et al. Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus. J Eur Acad Dermatol Venereol 2015; 29: 1718–1723.
38. Gholam P, Bosselmann I, Enk A, Fink C. Impact of red versus blue light on tolerability and efficacy of PDT: a randomized controlled trial. J Dtsch Dermatol Ges 2018; 16: 711–717.
39. Grapengiesser S, Ericson M, Gudmundsson F, Larko O, Rosen A, Wennberg AM. Pain caused by photodynamic therapy of skin cancer. Clin Exp Dermatol 2002; 27: 493–497.
40. Arits AH, van de Weert MM, Nelemans PJ, Kelleners-Smeets NW. Pain during topical photodynamic therapy: uncomfortable and unpredictable. J Eur Acad Dermatol Venereol 2010; 24: 1452–1457.